Dietary restriction and insulinlike signalling pathways as adaptive plasticity

Dietary restriction and insulin-like signalling pathways as adaptive plasticity: A synthesis and re-evaluation

Authors: Regan, J.C.[1], Froy, H.[3], Walling, C.A.[2], Moatt, J.P.[2] & Nussey, D.H.[1,2]

[1]Institute for Immunology and Infection and [2]Institute for Evolutionary Biology, School of Biological Science, University of Edinburgh.

[3]Centre for Biodiversity Dynamics, Norwegian University of Science and Technology, Trondheim Norway.

Corresponding authors:

Jenny Regan and Dan Nussey, Ashworth Laboratories, The Kings Buildings, University of Edinburgh, Charlotte Auerbach Road, Edinburgh EH9 3FL. Emails: jenny.regan@ed.ac.uk; dan.nussey@ed.ac.uk

Abstract:

1. Dietary restriction (DR) under laboratory conditions generally extends lifespan and delays ageing across species as diverse as yeast, nematode worms, flies, and mice, and is underpinned by taxonomically conserved physiological pathways, notably the insulin-like signalling pathway (IIS). Despite growing excitement about the links between DR / IIS and ageing within biogerontology, our understanding of why the DR response and associated pathways evolved under natural selection remains controversial and limited.
2. Here, we provide a brief overview of current understanding of the relationship between DR and IIS and ageing from modern biogerontology, and go on to summarise the evidence that the IIS pathway integrates a range of important environmental cues including photoperiod, temperature and humidity, as well as nutrition.
3. We go on to discuss the main existing evolutionary explanations for DR and argue that they are not mutually exclusive and are too nutrition-focussed to fully explain the evolutionary origin of the IIS pathway. In the wild, environmental cues and pressures are dynamic and multivariate, and physiological pathways capable of integrating multiple predictive cues could be strongly favoured by natural selection.
4. We hypothesise that the IIS and related pathways evolved to detect and integrate a wide range of environmental cues (not just diet) that are predictive of important selective pressures in the wild. Available evidence suggests the pathway is capable of triggering a range of phenotypic responses, depending on the cues provided, ranging from profound physiological remodelling (e.g. diapause, aestivation, hibernation) associated with promoting survival through challenging environments, to more subtle responses to acute, fine-scale variation in the environment which may allow individuals to better match their level of reproductive investment to their conditions.
5. We argue that the IIS pathway underpins important adaptive phenotypic plastic responses to a wide range of environmental inputs, of which diet is just one. A multi-disciplinary approach combining perspectives and methods from bio-gerontology, cell biology, ecology and evolutionary biology will be essential to develop our understanding of the evolutionary origins of this pathway and the way natural

selection and the environment have shaped variation in pathway's response to different environmental cues.

Key words: cues; natural selection; nutrient sensing; phenotypic plasticity; photoperiod; mechanistic target of rapamycin (mTOR); wild animals.

1. Introduction

Ageing, the deterioration of physiological function during adulthood, is a hugely complex and variable process with devastating consequences for organismal health. It has historically been viewed as both an intractable medical challenge in humans and as largely irrelevant to fitness in natural populations of animals (Alic & Partridge, 2011; Nussey, Froy, Lemaitre, Gaillard, & Austad, 2013). In the last two decades or so, both of these conceptions of the process have been spectacularly over-turned. Within biogerontology, a range of cellular processes have been identified as key players in organismal ageing (Lopez-Otin, Blasco, Partridge, Serrano, & Kroemer, 2013). Furthermore, a number of important and evolutionarily conserved genetic pathways have been found to directly influence lifespan and ageing phenotypes in laboratory animals, raising the possibility of developing clinical interventions that genuinely slow or delay senescence in humans (Partridge 2010). At the same time, a large and growing number of long-term, individual-based field studies demonstrate that ageing is widely observed in wild animals and can play an important part in evolutionary and ecological dynamics (Nussey et al., 2013; Robert, Chantepie, Pavard, Sarrazin, & Teplitsky, 2015; Colchero et al., 2019). One of the most robust and widely studied interventions impacting lifespan and ageing in laboratory studies is dietary restriction (DR; (Fontana, Partridge, & Longo, 2010; Speakman & Mitchell, 2011; Simpson et al., 2017)). Across species as diverse as yeast, nematode worms, flies, and mice, the consistent reduction of food intake in adulthood generally extends lifespan and reduces or delays the onset of ageing phenotypes. Many of the key genetic and physiological pathways that impact lifespan and ageing in the lab are so-called 'nutrient-sensing' (NS) pathways and are implicated in triggering the DR response (Fontana et al., 2010). To date, the prevailing evolutionary explanation is that the response reflects a form of adaptive phenotypic plasticity which promotes fitness by allowing the organism to survive challenging, food limited environmental conditions (Flatt & Partridge, 2018; Shanley & Kirkwood; Holliday 1989). Despite the considerable ongoing research efforts to understand the mechanisms involved under laboratory conditions, surprisingly little consideration has been given to the coevolution of plasticity, life history and ageing or the evolutionary forces which might have shaped and conserved both the DR response and NS pathways under natural conditions. Here, we briefly introduce some key concepts relating to the evolution of phenotypic

plasticity, before we move on to discuss a novel, synthetic perspective on what the DR response and NS pathways actually represent in ecologically and evolutionarily realistic contexts.

Phenotypic plasticity is usually defined as the ability of a single genotype or individual to express different phenotypes under different environmental conditions (Pigliucci, 2001). This definition encompasses two conceptually distinct responses to the environment, which are not mutually exclusive. The first reflects the environment *acting on* an organism's physiology to alter phenotype, and can encompass effects as apparently trivial as rising temperature increasing the rate of enzymatic reactions and organism-wide metabolism. Such effects are often referred to as environmental 'constraints' in the ecological literature. Unsurprisingly, this form of plasticity is extremely widespread in nature and largely reflects eco-physiological responses to environmental variation. The second type of plasticity arises through the evolution of sensory and endocrine apparatus to detect information and cues in the environment and trigger selectively beneficial physiological and phenotypic responses. We refer to this form of plasticity as 'predictive' plasticity, as it involves the organisms *reacting to* information in the environment. Both types of plasticity can potentially be adaptive, if past natural selection has acted to shape the genetic variation underpinning the response to the environment (Pigliucci, 2001). There are many classical examples of adaptive plasticity; for example, profound developmental switches in response to cues of predator presence that result in the development of armour or spikes in water fleas (Tollrian, 1995), and passerine birds altering their timing of egg laying in response to spring temperature in order to maximise food availability for their offspring (Phillimore, Leech, Pearce-Higgins, & Hadfield, 2016). Predictive plasticity can be considered as irreversible and fixed once a response has been triggered (as in the case of the morphological defences in water fleas) or reversible, with individuals capable of switching phenotypes repeatedly in response to environmental variation (as in the case of passerine egg laying).

Importantly from an evolutionary perspective, 'predictive' plasticity implies separation between the environmental cue an organism uses to trigger a phenotypic response and the environmental selective agent which affects fitness. Indeed, the cue and selective agent could be quite different aspects of the environment, for example when temperate organisms use photoperiod to trigger phenotypic changes to better cope with the challenges of winter. Or the cue may reflect the selective agent but be temporally separated; for example,

subtle changes in temperature acting as a cue for oncoming cold stress. On the other hand, 'constraint-based' plasticity implies that the environmental selective agent is the immediate, direct physiological cause of the plastic response. Evolutionary theory highlights a number of important considerations when thinking about how and why an apparently adaptive predictive form of plasticity evolved. First, predictive plasticity is generally expected to have fitness costs as well as benefits, and these may include time / energy costs of getting information from the environment, resource costs of using the sensing / endocrine machinery and physiological costs of actually mounting the phenotypic response (Auld, Agrawal, & Relyea, 2010; Dewitt, Sih, & Wilson, 1998). The evolution of plasticity also depends crucially on the availability of genetic variation in the phenotypic response to the environment (genotype-by-environment interactions, or G x E). If all genotypes in a population respond to the environment in an identical way (regardless of whether this is adaptive or not), then there is no G x E and no genetic variation in plasticity upon which natural selection can operate. Another important consideration in evolutionary models of plasticity is the reliability of the cues used to predict environmental selection and the fitness costs of mismatching phenotype and environment (Chevin & Lande, 2015; Ratikainen & Kokko, 2019). Predictive plasticity can presage physiologically unavoidable environmental challenges and allow the organism to maximise fitness under variable conditions (Chevin & Lande, 2015). This idea is important in the context of DR, because in laboratory studies we usually only consider responses to a focal environmental cue and rarely expose the organism to the environmental conditions which the response has evolved to predict. Furthermore, whilst most theoretical and empirical work in this area focuses on a single environmental cue and the response to it, there is growing awareness that selection may act to favour predictive plasticity to multiple environment cues (Chevin & Lande, 2015). Recent theory demonstrates that when predictive plasticity has evolved in response to multiple cues, results of studies focussing on a single environmental cue can be counter-intuitive and misleading (Chevin & Lande, 2015).

Despite there being a long-standing and well-established theoretical literature on the evolution of ageing (Hamilton, 1966; Rose, 1994), it is notable that very little theoretical attention has been paid to the evolutionary interplay between lifespan, ageing and phenotypic plasticity (Fischer, van Doorn, Dieckmann, & Taborsky, 2014; Flatt, Amdam, Kirkwood, & Omholt, 2013; Ratikainen & Kokko, 2019). Furthermore, a

coherent synthesis of evolutionary hypotheses put forward to explain DR and NS pathways in the lab is lacking. Here, we propose that the evolutionary conservation of both the DR response and associated genetic/endocrine pathways that have been found to regulate lifespan and ageing in the lab can be explained in terms of a very general form of adaptive predictive plasticity. We argue that this predictive response integrates diverse forms of environmental information and allows animals to alter their physiology to varying degrees. These alterations can both promote survival through periods of serious environmental challenge, and ensure appropriate investment in growth and reproduction, to maximise fitness under variable environmental conditions. Our hypothesis builds from syntheses presented by others (Flatt et al., 2013; Tatar & Yin, 2001), which provide compelling evidence that in a range of invertebrates, including widely studied laboratory nematodes and flies, multivariate changes in the environment predictive of sustained environmental challenges (e.g. onset of winter or dry season) trigger various kinds of diapause. They argue both that these responses represent an important form of adaptive predictive plasticity, which promote survival at the expense of growth and reproduction, and that the endocrine pathways involved in regulating this response include key NS pathways implicated in the response to DR.

Below, we first present our current state of knowledge on the DR response and NS pathways which may underpin it, before discussing evidence that a particularly important NS network – the insulin / insulin-like growth factor signalling and mechanistic Target Of Rapamycin pathways (IIS/mTOR) – actually acts to integrate a remarkably broad suite of environmental inputs, in addition to diet. We go on to review and attempt to synthesize existing evolutionary hypotheses to explain the DR response in lab animals, before presenting a more general hypothesis. This views the IIS/TOR pathway as an integrator of multiple environment inputs which ultimately triggers shifts in anabolic versus catabolic cellular activity along a continuum from acute responses to fine-scale variation in environmental quality through to profound physiological remodelling in response to cues for sustained environmental hardship. We end by discussing how this hypothesis might be tested in both lab and field, along with the need for more theoretical and empirical effort to understand the potential for coevolution among plasticity, life history and ageing.

2. Dietary restriction and IIS/TOR: Conserved pathways shaping lifespan in the lab

2.1. Dietary restriction: Laboratory-based research into the impact of DR on lifespan has a long history. In 1935, it was reported that restriction of calories without malnutrition extended the median and maximum lifespan of rats, when compared with *ad libitum* feeding (McCay, Crowell, & Maynard, 1935). This was closely followed by reports that DR could ameliorate other pathological features of ageing, including the development of spontaneous tumours (McCay, Maynard, Sperling, & Barnes, 1939; Tannenbaum, 1942), and the value of this manipulation for biogerontological research was first recognised (McDonald & Ramsey, 2010). DR remains the only known non-genetic manipulation that can extend lifespan in all species tested so far, including; yeast, the roundworm *C. elegans*, diptera including *Drosophila*, killifish, guppies, rodents, dogs and rhesus monkeys (Fontana et al., 2010). Empirical demonstration of the promotion of longevity by DR across a broad range of taxa has strengthened the argument for the strong evolutionary conservation of mechanisms involved in the DR response (Flatt & Partridge, 2018).

The term 'dietary restriction' encompasses a diverse range of dietary manipulations in the laboratory involving a range of study species. The most widely studied manipulation is classical caloric restriction, where calorie intake is restricted through either feeding a restricted food portion, dilution of a specific diet, or temporal restriction of food availability (reviewed in Speakman & Mitchell (2011)). However, DR is also used to describe macronutrient manipulations, *ad lib* feeding of a diet with a specific macronutrient content, and comparing the effects of a range of different macronutrient compositions (Lee, 2015; Moatt et al., 2017). These methodological differences and lack of consistency is a major challenge in the field of DR and makes cross-study comparisons difficult, even within the same species. However, significant steps to improve the consistency between studies has been made with the advent of nutritional geometry (Simpson et al., 2017) and elemental diets (Piper et al., 2014; 2017). It is also worth noting that laboratory studies within biogerontology have tended to focus on the effect of DR on lifespan, using this as a proxy for ageing. Recent studies do suggest that DR delays or ameliorates diverse phenotypes associated with ageing, including tissue pathology (Regan et al., 2016; Resnik-Docampo et al., 2017), body condition (Moatt et al., 2019), decline in metabolic (Solon-Biet et al., 2014) and immune (Miller et al., 2005) systems, and susceptibility to infection (Ponton et al., 2011). Inconsistencies in dietary manipulation and outcome measures notwithstanding, there

167 is now overwhelming evidence from laboratory studies that DR robustly extends lifespan and appears to
168 delay ageing across distantly related animal species.

169 *2.2 IIS and mTOR pathways:* A resurgence of studies on DR and ageing in the latter part of the 20th century
170 (McDonald & Ramsey, 2010) came in hand with the first reports of genetic deletions that could spectacularly
171 extend lifespan in nematode worms (Klass, 1983). Importantly, several of the mutations that extended
172 lifespan in worms were found to be in genes encoding for elements of pathways that respond to nutrient
173 intake (so-called 'nutrient sensing' pathways). These include the insulin-like signalling (IIS) pathway and the
174 mechanistic Target of Rapamycin (mTOR) pathway (Kapahi, Kaeberlein, & Hansen, 2017). The ability of
175 lowered signalling through these pathways to also extend lifespan in yeast (mTOR only), flies, and rodents,
176 suggested conservation of mechanisms across evolutionarily distant taxa (Fontana & Partridge, 2015).

177 What are the IIS and mTOR pathways, and what is their connection with diet? Broadly speaking, they are
178 signalling pathways that respond to inputs including nutrient levels in cells and tissues, and regulate the
179 switch between the energetically expensive building up of molecules and tissues (anabolism) and energy
180 releasing / conserving molecular breakdown (catabolism; Figure 1). These pathways are strongly conserved:
181 the mTOR pathway regulates energetics in single-celled eukaryotes through to mammals; while IIS ligands
182 are present as insulin-like peptides (ILPs) in arthropods, and insulin / IGF-1 in vertebrates. In vertebrates,
183 insulin is a major anabolic hormone: its release is induced by high blood glucose, it stimulates glucose
184 absorption into cells, and promotes glycogenesis and lipogenesis. It induces many other anabolic processes,
185 such as DNA replication and protein synthesis, and inhibits proteolysis and cellular recycling processes such
186 as autophagy (Figure 1). ILPs, signalling through the insulin receptor (InR/daf-2), perform comparable
187 functions in flies and worms (Nassel & Vanden Broeck, 2016). Insulin-like Growth Factor-1 (IGF-1), a hormone
188 closely related to insulin, is a major promotor of organismal growth in vertebrates. While arthropods do not
189 possess IGFs, they have growth-regulating steroid hormones (ecdysone and juvenile hormone) that are
190 regulated by IIS. mTOR is a protein kinase that forms two distinct multi-protein complexes named mTOR
191 complex 1 (mTORC1) and 2 (mTORC2). The mTORC1 pathway integrates inputs from intracellular and
192 extracellular cues, including growth factors, stress signals, energy status, oxygen, and amino acids, to control
193 anabolic processes including protein and lipid synthesis, cell growth, and cell cycle progression (Figure 1).

Growth factors that regulate mTOR include insulin and IGF (in mammals; ILPs in arthropods), acting through cognate effector kinases. Indeed, IIS and mTOR cross-regulate each other at several levels, and are more accurately described as a network than as distinct pathways (Laplante & Sabatini, 2012).

IIS/mTOR respond to DR and mediate many of its downstream effects. In a plethora of studies subjecting rodents to DR, circulating levels of insulin and IGF-1 were shown to be lowered, remaining so throughout the diet restriction period (Speakman & Mitchell, 2011). Calorie-restricted rhesus monkeys (Mattison et al., 2017), and humans taking part in randomized, controlled DR trials (Das, Balasubramanian, & Weerasekara, 2017), showed lowered insulin and IGF-1, improved glucose homeostasis, and increased insulin sensitivity. Concordantly in flies, systemic dILP release by insulin-producing cells (IPCs) in the brain is virtually abolished under DR, regulated via mTOR signalling in fat body cells (Geminard, Rulifson, & Leopold, 2009). FOXO/daf-16, a major downstream transcription factor of the IIS pathway (Figure 1), conserved from worms to mammals, is inhibited by high insulin/ILPs under full feeding conditions, and is activated by DR, mediating many of downstream effects of DR, such as autophagy and cellular protective mechanisms (Webb & Brunet, 2014; Webb, Kundaje, & Brunet, 2016). Similarly, lowered signalling through mTORC1, which regulates a broad suite of responses to changes in nutrient levels, is required for the full lifespan extension observed under DR in yeast, worms, and flies (Johnson, Rabinovitch, & Kaeberlein, 2013). Notably, other endocrine systems are affected by DR, including leptin, adiponectin, and ghrelin in rodents, for example (Speakman & Mitchell, 2011), and these are highly likely to be required for some of its downstream physiological effects. The involvement of other signalling pathways is one probable reason why phenotypes under DR are not fully recapitulated by genetic manipulations or drug treatments specifically targeting the IIS/mTOR network (Garratt, Nakagawa, & Simons, 2016).

Despite the common use of the term, IIS/mTOR are not truly ‘nutrient sensing’, but are higher-order pathways that communicate nutrient status to the body to dictate physiological responses (Mirth & Piper, 2017). Changes in nutrient availability are directly monitored within cells by molecular sensors that bind metabolic by-products of macronutrients, such as glucose metabolites from ingested carbohydrates, amino acids from proteins, and fatty acids from lipids (Efeyan, Comb, & Sabatini, 2015). The status of nutrient

concentration is then communicated to the rest of the body via systemic signals, such as the IIS/mTOR network.

Importantly, these pathways respond to environmental variation in a manner consistent with a predictive plastic response. Not only are they induced in response to immediate nutrient status as communicated by true molecular sensors, but can also be activated *predictively*, such that their upregulation can be induced by cues that *anticipate* a change in nutrient status. An example of this in mammals is the ability of taste receptors to activate mTORC1 in response to a rise in levels of extracellular (or gut luminal) amino acids without change in intracellular amino acid levels – an anticipatory mechanism for increasing anabolism in response to sensing ingested protein (Wauson et al., 2012). Similarly, in *C. elegans*, several olfactory and chemosensory neurons regulate the secretion of insulin-like peptides, where stimulation of these neurons in the absence of nutrients is able to induce IIS activation (Fontana & Partridge, 2015; Kenyon, 2005). As such, IIS/TOR are predictive pathways that respond to both immediate nutrient status within tissues, and predicted changes in nutrient status as communicated by other sensory systems. In response to high nutrient levels, or their predicted increase, signalling through the IIS/TOR network induces anabolic processes at both the molecular level (glycogenesis, lipogenesis) and tissue level (cell growth and division; Figure 1). Conversely, low nutrient abundance induces a rapid switch by attenuation of these pathways towards catabolic processes such as nutrient recycling and limited growth (Figure 1). It has been hypothesised that this predictive plastic response, underpinned by IIS/mTOR pathways, meets a fundamental need for organisms to match energetically expensive actions such as growth and reproduction with environmental nutrient availability and, as such, has been strongly favoured by natural selection and broadly conserved across taxa (Flatt et al., 2013; Laplante & Sabatini, 2012).

Our understanding of the function and fitness costs and benefits of the DR response and IIS/mTOR pathways under natural conditions is currently limited. Understandably, within biogerontology, the focus is generally on translation to humans in a clinical setting, and the goal is interventionist delay of ageing through the identification of druggable targets (Vaiserman, Lushchak, & Koliada, 2016). There is a strong argument that laboratory conditions are effective at modelling human health and ageing in developed countries, given our temperature-controlled living environments, relative lack of pathogen challenge, and '*ad libitum*' eating

habits. However, studies in model organisms in controlled laboratory conditions fall short when it comes to testing ideas about the evolution of the DR response and IIS pathways in the wild for several reasons. First, laboratory animals are very rarely raised on diets that resemble those available in the wild (although see Moatt et al. (2019)) and, in addition, often have unlimited access to food. This has been used to support the argument that lifespan extension by DR in lab animals is simply the result of curbing the damaging effects of obesity, or an otherwise toxic diet (Adler & Bonduriansky, 2014; Speakman & Mitchell, 2011). Second, inbred, lab-adapted animals may have been selected for rapid growth, and early or high fecundity, and therefore their physiological responses to DR may not reflect those of wild populations (Austad & Kristan, 2003). Third, DR regimes are usually chronically maintained over the life course and consider the manipulation of only one component of the environment (food). This is unrepresentative of natural populations in which nutrient availability typically varies dramatically in space and time and is accompanied by many other environmental cues and challenges (e.g. cold, parasites, competition, and water availability). Finally, in the laboratory the manipulation of dietary cues is not accompanied by any form of selective pressure, unlike in the wild where a change in food availability may be accompanied by, or presage, a series of environmental challenges exerting natural selection on any phenotypically plastic response. This makes assessing the fitness costs and benefits of a particular plastic response associated with IIS/mTOR signalling from standard laboratory studies very challenging.

Given the essential role for communication of nutrient status by IIS/mTOR, and the comparable effect on lifespan to DR by their genetic attenuation, the nutrient-sensing role for these pathways have generally been the point of focus in biogerontology (Alic & Partridge, 2011; Johnson et al., 2013). However, there is mounting evidence that these pathways integrate many more cues than just nutritional status, and increasing appreciation of their likely evolutionary significance as regulators of predictive plasticity. To better understand the evolutionary significance of DR and IIS/mTOR signalling, we focus on three broad but largely unanswered questions:

1. What are the environmental cues that IIS/mTOR pathways have evolved to respond to?

2. What are the fitness benefits of the plastic response regulated by IIS/mTOR *in the wild*, and what are the selective pressures that the plastic response has evolved to match phenotype/life history to?
3. Are there likely to be costs of this plasticity in the wild that could also impact how selection acts?

3. Environmental cues: IIS/TOR pathways are responding to more than just diet

It is clear that IIS/TOR pathways are exquisitely sensitive to changes in nutrient levels, and play a pivotal role in regulating physiological responses to these changes. However, there is also abundant evidence they are integrating and responding to a very broad suite of environmental cues, in addition to nutrient status, all of which could predict very significant aspects of environmental pressures on wild animals. These 'other' cues have been largely side-lined in debates over the adaptive nature of these pathways. We suggest that in order to properly understand the phenotypic plasticity regulated by these pathways, the integration of other cues must be considered. Presented as a table below, are environmental cues, apart from nutrition, that have been demonstrated to impact IIS/mTOR signalling to modify physiology in lab studies or in agricultural / aquacutural settings.

296 **Table 1 – Environmental cues integrated by IIS/mTOR.** FOXO (Forkhead box O): transcription factor;Hif-1:
297 Hypoxia-inducible factor 1; IGF-1/2: insulin-like growth factor 1/2; ILP: insulin-like peptide; JNK: c-Jun N-
298 terminal kinases; Ppk28 (Pickpocket28): a water-sensing protein; REDD1/2: regulated in development and
299 DNA damage response 1/2. Note that all examples are in response to artificial not natural cues.

300

Cue	***Species***	***IIS/mTOR component***	***Up/downstream molecular regulation***	***Physiological response***	***References***
Photoperiod (day length)	The mosquito, *Culex pipiens*	IIS / FOXO	Juvenile hormone (JH)	Adult (reproductive) diapause	(Sim & Denlinger, 2008; Sim, Kang, Kim, Bai, & Denlinger, 2015)
	Teleost fish e.g. rainbow trout, salmon	IGF-1		Progression from adolescence to spawning	(Taylor, Migaud, Porter, & Bromage, 2005; Taylor, Porter, Bromage, & Migaud, 2008)
	Dairy cattle	IGF-1		Lactation	(Dahl, Buchanan, & Tucker, 2000; Peters, Chapin, Leining, & Tucker, 1978)
Photoperiod + temperature	*Drosophila*	IIS / dILP1 / dILPs 2-5	JH	Adult diapause	(Kucerova et al., 2016; Liu, Liao, Veenstra, & Nassel, 2016; Ojima, Hara, Ito, & Yamamoto, 2018; Schiesari, Andreatta, Kyriacou, O'Connor, & Costa, 2016; Schiesari, Kyriacou, & Costa, 2011)
Circadian rhythm (day/night)	*Drosophila*	IIS / mTOR		Night sleep (FOXO) Daytime activity (mTOR)	(Metaxakis et al., 2014)
	Human cell lines	mTOR	Mg^{2+}	Cellular energetics (ATP)	(Feeney et al., 2016)

Temperature	*Drosophila*	IIS		Adult diapause	(Anduaga, Nagy, Costa, & Kyriacou, 2018; but see (Nagy et al., 2018))
	Drosophila	IIS		Body size	Li, Q. & Z. Gong, 2015)
	Rainbow trout, *Oncorhynchus mykiss*	IGF-1	Growth Hormone (GH)	Progression from adolescence to spawning	(Gabillard et al., 2003)
	Garter snake (*Thamnophis elegans*)	IGF-1 / IGF-2		Growth	(Reding, D. M., *et al* 2016)
Water	*Drosophila*	FOXO	Ppk28	Metabolic regulation, ageing, longevity	(Waterson et al., 2014)
Salinity	Golden spiny mouse	(insulin)	vasopressin	Reproductive repression	(Shanas & Haim, 2004)
	Gilthead sea bream (*Sparus aurata)*	IGF-1		Osmotic acclimation	(Mohammed-Geba, K., Mancera, J.M. & Martínez-Rodríguez, 2015)
Oxygen	Mouse	mTOR	Hif-1; REDD1 and REDD2	Growth regulation	(Brugarolas et al., 2004)
	Drosophila	mTOR	Hif-1	Growth regulation	(Reiling & Hafen, 2004)
Infection / immune challenge	*Drosophila*	IIS	Toll, JNK	Increased immune response, decreased energy stores & growth	(DiAngelo, Bland, Bambina, Cherry, & Birnbaum, 2009; Wang, Bohmann, & Jasper, 2005)

3.1. Non-dietary cues and the IIS/mTOR pathway: Sensing changes in photoperiod is essential to organisms in non-equatorial regions that need to time physiological events to predictable, annual changes. This is of fundamental importance to overwintering mammals and insects, who change their physiology dramatically through hibernation, torpor, or diapause to survive challenging conditions, and who must also reverse metabolic depression in readiness to reproduce as conditions improve (Hut, Dardente, & Riede, 2014). There is growing evidence in insects that the IIS pathway is sensitive to photoperiod changes, and is involved in regulating downstream physiological responses (reviewed in (Flatt et al., 2013; Sim & Denlinger, 2013; Wu & Storey, 2016)). In *Drosophila*, IIS controls the entry into adult diapause (essentially a reversible state of reproductive arrest, also referred to as reproductive dormancy) in concert with the steroid Juvenile Hormone (JH). The IIS/JH axis responds to short photoperiod in combination with lowered temperatures in fruit flies (Kucerova et al., 2016; Liu et al., 2016; Ojima et al., 2018; Schiesari et al., 2016; Schiesari et al., 2011), and similarly, controls overwintering adult diapause in the mosquito *Culex pipiens* (Sim & Denlinger, 2008; Sim et al., 2015). Entry into diapause in *C. pipiens* requires activity of FOXO (Sim & Denlinger, 2008; Sim et al., 2015), a transcription factor activated upon low IIS (Figure 1). Neural light-sensing mechanisms in insects induce hormonal cascades in response to changing photoperiodicity (Schiesari et al., 2011), which regulate IIS (Stenvers, Scheer, Schrauwen, la Fleur, & Kalsbeek, 2019). Although steps in the pathway leading from perception of daylength to generation of the adult diapause phenotype are just beginning to be unravelled (Andreatta, Kyriacou, Flatt, & Costa, 2018; Ojima et al., 2018), IIS regulation of steroid hormones including JH, which control developmental transitions in holometabolous insects, is key. In addition to these complex endocrinological networks, simpler photo-sensitive molecular oscillators exist. For example, light-driven, circadian Mg^{2+} oscillations directly regulate mTOR in mammalian cells through to algae (Feeney et al., 2016), linking metabolism and growth to circadian, and potentially photoperiodic, cycles (van Ooijen & O'Neill, 2016). Given the extent of IIS/mTOR cross-regulation, this presents a potential mechanism for direct transmission of photoperiodic information by mTOR to IIS-regulated processes (e.g. Metaxakis et al., 2014).

Ruminant mammals in temperate zones time reproductive events by photoperiod to ensure young are born in spring/summer and not during challenging seasons (Zerbe et al., 2012). Lactation in cows has been demonstrated to be sensitive to photoperiod (Peters et al., 1978), and artificial long day lengths are employed

as a reliable method to boost milk production in dairy cattle (Dahl et al., 2000). Studies have shown that IGF-1 is sensitive to photoperiod in cows, is galactopoietic, and mediates the lactation response to long photoperiod (Dahl, 2000). In teleost fish such as rainbow trout and salmon, IGF-1 levels have also been shown to be regulated by photoperiod (Taylor et al., 2005; Taylor et al., 2008), and determine progression from adolescence to spawning. Empirical data exists for these two species due to the economic importance of maximising output in fisheries/farming industries; nonetheless, the fact that very different species (e.g. teleost fish and cows) are demonstrated to have photoperiod-sensitive IGF signalling regulating features of reproduction, suggests that this could be a general feature across vertebrates. Animals in habitats that do not have large photoperiodic shifts, or in environments where photoperiodicity does not predict seasonal change such as wet/dry, need to time life history events using other cues. In arid environments where water is limiting, animals modify their metabolism and transition to reproductive arrest during dry periods (Geiser, 2010), for example, the desert-dwelling golden spiny mouse, responds to dietary salinity to repress reproduction, via vasopressin (Shanas & Haim, 2004), which is known to respond to insulin and blood glucose levels (Nakamura, Velho, & Bouby, 2017).

Ectothermic reptiles, such as snakes and lizards, which demonstrate high metabolic flexibility, regulate IGF-1, and consequently growth, in response to temperature shifts (Sparkman, Byars, Ford & Bronikowski, 2010). For example, there is evidence for the regulation of both growth and reproduction by IGF-1 in response to temperature in the brown house snake, *Lamprophis fuliginosus*, suggesting a key role for IGF-1 in determining ecotypes with different life history strategies (Sparkman, Byars, Ford & Bronikowski, 2010). Furthermore, the act of mating itself can induce physiological changes regulated by IIS. In *L. fuliginosus*, IGF-1 peaks rapidly after first mating, and in addition, positively correlates with increased feeding rates (Sparkman, Byars, Ford & Bronikowski, 2010), potentially predictively linking nutrient intake with anticipated reproductive effort. In *Drosophila*, the absorptive capacity of the intestine is predictively changed by mating, by increasing cell size and intestinal stem cell division, and increasing lipid metabolism in enterocytes. This occurs not in response to changes in nutrients and/or the demands of egg production, but preceding them (Reiff et al., 2015), and this organ size plasticity increases fecundity. Mating-induced gut growth is induced by JH, and both JH release and intestinal stem cell division are regulated by IIS (O'Brien, Soliman, Li, & Bilder, 2011; Rauschenbach et

al., 2017; Tu, Yin, & Tatar, 2005). This is particularly interesting, as mating should be a good cue that an organism needs to mobilise resources for reproductive investment. Plastic gut growth to support lactation (or in response to intermittent feeding) is a common feature in small mammals, particularly those with large litter sizes (Carey, 1990; Dunel-Erb et al., 2001). The endocrine axis triggering this is not known, but the role for IGF-1 in adult intestinal growth in mammals (Howarth, Cool, Bourne, Ballard, & Read, 1998; Van Landeghem et al., 2015) demonstrates conservation of IIS-signalling in remodelling gut physiology.

Arresting reproduction and growth to avoid periods of pathogenic challenge is also regulated through IIS/mTOR in insects (Schwenke, Lazzaro & Wolfner, 2016). Activation of both Toll (broadly induced by gram positive bacterial and fungal infection) and JNK (induced by stress and immune challenge) pathways reduces IIS in flies (Wang et al., 2005; DiAngelo et al., 2009). Indeed, immune pathways and IIS/TOR are reciprocally antagonistic, where FOXO activity upon low IIS increases transcription of immune genes (Becker *et al* 2010), as does low mTOR via the activity of a related TF, Forkhead (Varma, Bülow, Pesch, Loch, & Hoch 2014). In fact, IIS mutant flies resist infection better than their non-mutant controls (Libert, Chao, Zwiener, & Pletcher 2008). Reciprocal regulation of IIS and pathogen-sensing systems may predictively conserve energy in anticipation of a sustained immune challenge; and conversely, during periods of low nutrient intake, upregulate immune defence genes prophylactically (Schwenke et al., 2016). Indeed, upregulation of immune response genes, including certain antimicrobial peptides, has been demonstrated during adult diapause in *Drosophila* (Kubrak, Kucerova, Theopold, & Nassel, 2014).

3.2. Multiple cue integration by IIS/TOR: In the wild, environmental challenges will rarely occur in isolation. Food and water scarcity, extremes of temperature, and parasite challenges often come in complex, but potentially predictable multivariate packages. In temperate regions, seasonal changes are predictable, if somewhat variable in onset, force, and duration. The ability to predictively sense and respond to seasonal and within-season fluctuations with appropriate metabolic and reproductive strategies should increase fitness. Considering this, it makes sense that selection would favour pathways that respond in an integrative way, and respond in a similar way to multiple different cues. Winter is an obvious example of a combined

386 package of environmental stresses: cold temperatures, high humidity and food scarcity. Animals approaching
387 winter need to predict its arrival well in advance to implement preparatory strategies such as increased
388 appetite and coat growth. It should also be advantageous to respond to more subtle fluctuations such as a
389 warm autumn, or an early-onset winter. These fluctuations may not be sufficiently communicated by a single,
390 fixed cue, such as photoperiod (Kumar et al., 2010), and may be why initiation into reproductive arrest in
391 overwintering insects requires the combination of thermal and light cues, for example (Schiesari et al., 2011).
392 Emergence from challenging seasons must also be appropriately timed; both with respect to reversal of
393 metabolic depression strategies, and resuming reproduction, both of which will have disastrous
394 consequences for fitness if initiated too soon. Combinatorial cue sensing will be crucial in this context, where
395 the onset of favourable conditions may be highly variable year on year.

396 The importance of particular cues will change depending on the environment; e.g. using temperature and
397 rainfall, but not photoperiod, will be important for equatorial species, as is the case for the regulation of
398 reproduction in the arid zone passerine bird, the sociable weaver (Mares, Doutrelant, Paquet, Spottiswoode,
399 & Covas, 2017). Some animals take an opportunistic breeding strategy when favourable conditions are highly
400 unpredictable, such as the Darwin's finch, *Geospiza fuliginosa*, which responds to changes in barometric
401 pressure, humidity and water availability to increase gonad size and breed opportunistically after rain (Hau,
402 Wikelski, Gwinner, & Gwinner, 2004).

403 Although environmental cue integration has been empirically demonstrated in diverse species (e.g. (Hau et
404 al., 2004; Liu et al., 2016; Phillimore et al., 2016; Schiesari et al., 2011)) our understanding of how this
405 integration occurs is very limited. For example, data from overwintering species strongly suggests that
406 IIS/TOR signalling is key to induction of metabolic repression (Flatt et al., 2013; Sim & Denlinger, 2013; Wu &
407 Storey, 2016), and that integration of photoperiod and thermal cues are important for its onset (e.g. Sim &
408 Denlinger, 2008; Sim et al., 2015). However, studies to elucidate the molecular basis for this integration are
409 so far lacking.

410 It is important to make the point here that the environmental cue(s) being sensed may or may not be the
411 environmental force that is being anticipated. For example, changes to photoperiod are likely not detrimental

412 in themselves to fitness, but act as a cue for oncoming temperature and weather changes. Similarly, changes
413 in available macronutrients, as might be modelled by a DR regime in the lab, may be acting as a cue for severe
414 food shortages at a later date. There is a clear need to understand how cues, that have so far been studied
415 in isolation in the lab, are being integrated by IIS/TOR, and what the associated fitness costs and benefits of
416 mounting the physiological responses to these cues are, under challenging or variable conditions.

417

418 **4. A synthesis of existing evolutionary explanations for the DR response**

419 In the previous sections, we outlined the DR paradigm and the conserved role of the IIS pathway in this
420 response and other aspects of organismal life history and then reviewed extensive evidence that IIS/TOR
421 integrate a very wide range of environmental cues, are far more than just 'nutrient sensing' pathways, and
422 are more correctly viewed as an 'environment-sensing' network. We now move on to review the main
423 hypotheses that have been put forward to explain the evolution and conservation of the DR response in the
424 laboratory, and ask how well supported these ideas are by currently available data. We argue that, although
425 sometimes set up as alternatives, these current hypotheses are in many respects complementary and can be
426 synthesised under a broader conceptualisation of the DR responses as a powerful form of predictive
427 plasticity.

428 The so-called resource reallocation hypothesis (RRH; Shanley & Kirkwood, 2000) explains the DR response
429 using ideas derived from the disposable soma theory of ageing (Kirkwood, 1977). This theory explains the
430 evolution of ageing as the result of resource allocation trade-offs between reproduction and somatic
431 maintenance. It argues that, since the force of natural selection weakens with age (Hamilton, 1966),
432 investment of limited resources in reproduction in early life should generally be favoured by selection over
433 investment in long-term organismal maintenance and homeostasis (Kirkwood, 1977). Importantly, the
434 degree to which early life reproduction is favoured over maintenance depends on the specifics of the
435 organism's life history and the environmental pressures it faces (Flatt et al., 2013; Shanley & Kirkwood, 2000).
436 Shanley & Kirkwood (2000) argued and illustrated with a dynamic resource allocation model that, during
437 periods of 'famine' (i.e. reduced resource availability), natural selection could favour a plastic switch in life

history allocation from reproduction to maintenance. This would allow organisms to survive through challenging periods, when the fitness pay-offs of reproduction could be low due to reduced offspring survival and the costs of reproduction could be raised due to poor environmental conditions, and then switch their resource allocation strategy back towards reproduction when environmental conditions improved (Shanley & Kirkwood, 2000). This hypothesis invokes a form of predictive plasticity in which the environmental cue is diet-related (resource availability) and the response is a switch in resource allocation from reproduction to maintenance or vice-versa. The selective benefit of the plastic response in the wild would lie in the ability to better survive periods of famine (when chances of successful reproduction are slim) and maximise reproductive output when conditions are favourable. Under standard DR laboratory conditions, this plastic response would mean that keeping animals on a restricted diet results in increased investment in maintenance and hence longer lifespan and a reduction in ageing phenotypes.

The fact that the lifespan increase under DR observed in the laboratory is commonly associated with reduced fecundity or even infertility has been interpreted as support for the RRH hypothesis (Ball, Barnes, & Visscher, 1947; Chapman & Partridge, 1996). Further support comes from evidence that manipulation of IIS/mTOR pathways dramatically affects growth and reproduction. Attenuated signalling through IIS/mTOR, achieved through either genetic manipulation, drug treatment or dietary restriction, is costly for reproduction (Alic & Partridge, 2011). For example, *Drosophila insulin receptor* (*InR*) hypomorphic mutants or InR-substrate *chico* mutants are sterile, presenting arrested egg development (Clancy et al., 2001; Tatar et al., 2001). Furthermore, *Drosophila InR* null mutants are embryonic lethal (Fernandez, Tabarini, Azpiazu, Frasch, & Schlessinger, 1995), illustrating the essential role for the IIS pathway during embryogenesis. The requirement for IIS/mTOR during development is conserved: mTOR mutant mice are early embryonic lethal (Murakami et al., 2004), and *Igf1r-/-* mice are severely growth restricted and die shortly after birth (Liu, Baker, Perkins, Robertson, & Efstratiadis, 1993). Furthermore, the extension of these disposable soma-related ideas to explain the wide range of diapause responses to more diverse environmental challenges in invertebrates (Flatt et al., 2013; Tatar & Yin, 2001) suggests broadly conserved pathways such as IIS may be involved in crucial predictive plastic responses which allow organisms to survive periods of challenging environmental conditions. A broad range of developmental and reproductive diapause and dormancy phenotypes across

taxa - including nematode worms, fruit flies, butterflies, grasshoppers and blow flies - appear consistent with adaptive predictive plasticity to down-regulate growth and reproduction to preserve survival prospects under severe environmental challenge (Tatar & Yin, 2001). Interestingly, the IIS pathways has been implicated in regulating these responses in many of these examples (Flatt et al., 2013; Tatar & Yin, 2001). Although not directly related to diet and the DR response, these examples lend strong support to the idea that predictive plastic responses which allow organisms to switch to physiological states that maximise survival prospects under environmental challenge are prevalent in nature.

However, recent evidence suggests the RRH does not offer a complete explanation for the observed DR response in the laboratory. For example, several studies have now shown that a DR response can be triggered without manipulating resource availability, by manipulating genetically or pharmacologically the signalling pathways underlying the response (e.g. IIS and mTOR: Fontana & Partridge, 2015). It has been argued that this undermines the RRH (Adler & Bonduriansky, 2014), although if the RRH response reflects an adaptive form of predictive plasticity that uses dietary inputs as cues to trigger resource allocation shifts then we would still expect to see a plastic response if the signalling pathways were manipulated without changing the dietary input. Perhaps more troubling is mounting evidence that the trade-off between reproduction and survival, which underpins the RRH, is not straightforward and can be circumvented under laboratory conditions such that DR responses can occur independent of any costs of reproduction (Dick, Ross, & Yampolsky, 2011; Grandison, Piper, & Partridge, 2009; O'Brien, Min, Larsen & Tatar, 2008; Mirth & Piper, 2017). Indeed, recent studies which allowed fruit flies populations to evolve for 50 generations under different constant dietary conditions showed that sex-dependent lifespan differences emerged between lines but these were not accompanied by expected antagonistic changes in fecundity, arguing against a role for resource reallocation trade-offs (Zajitschek et al., 2014; 2018). In our opinion, the evidence available does not necessarily preclude the fundamental idea encompassed by the RRH that the DR response and IIS/mTOR pathways evolved to allow organisms to maximise survival versus reproductive function under variable environments. However, evidence strongly suggests that the notion that this conserved plastic response is mechanistically driven by resource allocation trade-offs between these two aspects of an organism's life

history is overly-simplistic and does not fit with our current understanding of the physiological and cellular responses to DR and IIS/mTOR manipulation.

More recently, Adler & Bonduriansky (2014) pointed out that DR and reduction of IIS/TOR pathway signalling appears generally to dis-inhibit (up-regulate) autophagy / apoptosis and cellular recycling mechanisms, whilst up-regulation of these pathways and *ad lib* feeding inhibit those mechanisms and increase catabolic processes involved in cellular growth and proliferation. They argue that it is this switch between anabolic, cellular recycling function and catabolic cellular growth and proliferation function that underpins the DR response and the way IIS modulates longevity in the laboratory. While this is much more explicit about and in keeping with what we know about the physiology of the DR response and associated pathways than the RRH hypothesis, it remains at least potentially consistent in the sense that the response could still have evolved to switch physiological state towards greater maintenance (cellular recycling, autophagy) versus growth and reproduction (cellular growth and replication). When conditions are good and resources are plentiful (i.e. *ad lib* feeding conditions) it would make evolutionary sense to upregulate catabolic processes that promote cell replication and growth and, in turn, organismal growth and reproduction. However, Adler & Bonduriansky (2014) argue that, contrary to the RRH, the IIS and related pathways have not evolved to promote organismal survival under resource limitation / harsh environmental conditions. Despite considerable evidence that DR / IIS-inhibited animals are in many respects stress resistant in the laboratory (e.g. Broughton et al., 2010; Gronke, Clarke, Broughton, Andrews, & Partridge, 2010), they argue that that reduced catabolism under DR limits the ability to mount immune and wound-healing responses, tolerate cold temperatures, compete for resources and avoid predation, all of which would negatively impact chances of survival in the wild (Adler & Bonduriansky, 2014). They contend that the benefits of investing in somatic maintenance and cell/nutrient recycling processes are likely to be very limited under natural conditions due to generally high mortality, and that the DR response instead represents a mechanism to maintain the short-term ability to reproduce under challenging environmental conditions (Adler & Bonduriansky, 2014).

In our opinion, there are serious problems with this as a general explanation for the evolution and conservation the DR response and IIS pathway (see also Le Bourg, 2014). First and most strikingly, the assumption that the ability to survive challenging environmental conditions, even at cost to short-term

518 reproduction, offers little general selective benefit in the wild is clearly fallacious. It ignores the diverse forms
519 of facultative diapause in short-lived vertebrates, which promote survival during challenging conditions
520 through a temporary cessation of growth or reproduction, which are clearly adaptive and ubiquitous
521 (discussed above). Furthermore, it ignores the many forms of torpor and seasonal hypo-metabolism
522 observed in wild vertebrates which are widely accepted as adaptive mechanisms to promote survival by
523 reducing metabolism and diverse physiological functions going into times of extreme environmental hardship
524 (e.g. Signer, 2011; Turbill, Ruf, Mang, & Arnold, 2011). Animals do not grow or reproduce in these quiescent
525 states, but there has evidently been strong selection favouring the evolution of predictive plastic machinery
526 to trigger switches into these non-reproductive states. Secondly, while there is no doubt that mortality risks
527 are very different and generally higher in the wild than in the laboratory, the notion that short-term
528 reproduction is generally going to be favoured by natural selection over both short- and long-term survival
529 prospects seems very unlikely. There is very clear evidence from across a broad range of animal taxa that
530 senescence is both widely observed in the wild and can strongly impact the dynamics of natural populations
531 (Bonduriansky & Brassil, 2002; Nussey et al., 2013). There is strong ecological evidence that adult mortality
532 risk is under very strong selection and that adult survival is a key factor in the population dynamics of many
533 vertebrate systems (Colchero et al., 2019; Robert et al., 2015). Adler & Bonduriansky (2014) present their
534 hypothesis as a general explanation for the evolution of DR responses / IIS pathways that is in contrast to the
535 RRH. We see merit in its more explicit consideration of the cellular and physiological processes involved and
536 certainly can envisage circumstances under which a maintaining reproductive function under environmental
537 challenge might confer a fitness advantage in the wild. But we think current evidence argues that this cannot
538 provide a general explanation for the DR response / IIS pathway across organisms of differing life
539 expectancies experiencing wildly varying environmental conditions.

540 The RRH and Adler & Bonduriansky's hypothesis are both compatible with the DR response and IIS pathway's
541 involvement in lifespan extension being part of an evolutionarily conserved predictive plastic response to
542 environmental cues. However, many have argued that effects of DR under laboratory conditions reflect a
543 form of reactive plasticity or 'constraint'. Some have argued that *ad libitum* fed control groups may over-feed
544 and that their reduced lifespan reflects pathological health consequences of this over-eating relative to more

545 naturalistic feeding levels observed in DR groups (Speakman & Mitchell, 2011). More recently, research
546 exploring the role of different macro- and micro-nutrients in the DR response, have observed that fecundity
547 is maximised but survival is reduced under high relative protein intake (Grandison et al., 2009; Lee, 2015).
548 The emergent 'toxic protein' hypothesis states that while protein is required for reproduction, consumption
549 of too much protein has pathological consequences manifesting in reduced late-life health and lifespan (e.g.
550 (Fanson, Fanson, & Taylor, 2012). However, the suggestion of a physiological cost of protein ingestion is
551 overly simplistic. Whilst there is evidence consistent with high protein consumption being associated with
552 reduced lifespan, this only fits when specifically looking at protein intake relative to intake of other
553 macronutrients (Grandison et al., 2009; Lee, 2015; Maklakov et al., 2008; Solon-Biet et al., 2014) with
554 increasing evidence that the non-protein component of the diet can also have direct effects on lifespan (e.g.
555 (Jensen, Schal, & Silverman, 2015; Maklakov et al., 2008; Moatt et al., 2019). Furthermore, such a direct
556 physiological effect of protein on either reproduction or longevity does not offer any explanation for why a
557 cue and signal based system of predictive plasticity, such as the IIS pathway, would evolve. Lifespan extension
558 can be achieved purely through manipulation of the signalling pathways, which is not consistent with protein
559 having a direct, toxic effect on lifespan. That said, such passive plastic responses of organismal physiology to
560 variation in dietary input could play a major role in explaining observed effects of DR experiments in the
561 laboratory or responses to food intake in the wild, and could occur alongside predictive plastic responses
562 triggered by IIS signalling. It is also possible that relative levels of protein intake could be used by predictive
563 pathways (such as mTOR) as an environmental cue to trigger physiological switches that would allow
564 organisms to optimally time pulses of growth or reproduction with regard to protein availability in their
565 environment.

566

567 **5. A more general hypothesis for the evolution of DR pathways**

568 None of the existing theories, discussed in the previous section, provide a complete and satisfactory answer
569 to the question of why lifespan extending pathways such as IIS have evolved under natural selection, and
570 why they appear so conserved across distantly related animal taxa. In the laboratory, for obvious reasons,
571 we tend to manipulate single environmental variables and hold all else as constant as possible. The DR effect

572 on lifespan and ageing has emerged entirely from this approach with relatively little consideration of
573 ecological and evolutionary pressures that might shape such a response under natural conditions. We have
574 argued that the evolutionary conservation of IIS/mTOR pathways and experimental demonstration that their
575 effects on phenotype can be independent of dietary input strongly imply that these pathways underpin an
576 adaptive predictive plastic response. We have also synthesised the mounting evidence from laboratory
577 studies demonstrating that such pathways detect and respond to a great deal more than just nutrient intake,
578 and are most likely responding to integrated information from a broad range of environmental cues (see
579 Table 1).

580 In the wild, environmental variation is complex and multivariate with synchronous changes often occurring
581 in factors such as photoperiod, temperature, humidity, and food availability. The most obvious example is
582 seasonal changes in temperate regions, however comparable predictable and complex shifts in tropical (e.g.
583 dry / wet) regions. Importantly, the same kinds of environmental variables could provide important signals
584 to animals about spatial, daily, and annual variation in conditions. Our hypothesis is that the IIS/mTOR
585 pathway has evolved to detect and integrate a wide range of environmental cues (via networking with
586 downstream cellular sensing pathways and sensory organs), rather than solely as a 'nutrient sensing' pathway
587 as frequently implied in the biogerontology literature.

588 A critical question, and the real sticking point for existing explanations for the evolution of the DR response,
589 is the nature of the fitness pay-off under natural conditions of the predictive plastic response. The RRH posits
590 that selection favours the ability to survive at a cost to reproduction under challenging conditions (Shanley
591 & Kirkwood, 2000), whilst it has also been suggested that the ability to maintain current reproductive
592 function at a potential cost to future reproduction and survival could be strongly selected for (Adler &
593 Bonduriansky, 2014) when food supplies are limited. These ideas are rooted in a rather singular
594 conceptualisation of reproduction-survival trade-offs, rather than taking an evolutionary perspective on
595 phenotypic plasticity. At a cellular level, we understand that DR / suppression of the IIS pathway triggers a
596 switch from catabolic to anabolic states, with upregulation of cell recycling, autophagy and apoptosis (Adler
597 & Bonduriansky, 2014). Associated reductions in cellular growth and proliferation could well limit organismal
598 growth, reproduction, immune responses and would healing at considerable fitness cost to the organism

(Adler & Bonduriansky, 2014). But at the same time, under environmental stress and resource limitation, these same processes and their diverse metabolic costs could undermine an organism's ability to maintain homeostatic function and survive. To this point, we are simply reiterating the framework of the hypothesis of Adler & Bonduriansky, but as discussed above, we reject their contention that survival in the face of environmental pressure is of little general fitness value in the wild. Instead, we contend that the cellular response described is actually one end of a physiological continuum of responses, all entrained on the same kinds of environmental cues, which are capable of triggering diverse physiological and life history responses which would increase fitness under variable environmental conditions compared to an organism that was unable to respond plastically in the same way.

This hypothesized continuum of plastic response to environmental cues indicating general deterioration or improvement in the environment includes, at one extreme, the deep physiological remodelling associated with developmental and reproductive diapause, torpor and seasonal hypo-metabolism, which are widely observed in terrestrial animals (Flatt et al., 2013; Tatar & Yin, 2001; Wu & Storey, 2016). For example, larval diapause, or 'dauer' formation and pupal arrest in invertebrates are strategies to survive stressful conditions such as starvation, crowding, and temperature change (Flatt et al., 2013). In *C. elegans*, dauer larvae cease feeding and moving, harden their cuticle and change their metabolic profile. Developmental arrest phenotypes have long been known to be regulated by IIS: the unified C. elegans IGF/insulin receptor *daf-2*, and its effector transcription factor *daf-16* (FOXO) were originally identified as regulators of dauer formation before their role in lifespan determination was uncovered. Similarly, reproductive dormancy in Drosophila, a response hypothesised to facilitate over-winter survival in temperate regions, is regulated by IIS (Flatt et al., 2013; Wu & Storey, 2016). There are also clear examples of mammals switching towards a hypo-metabolic state to survive winter or periods of drought, for instance by hibernating through winter, or summer aestivation. Evidence also suggests that non-hibernating species, such as ruminants, show a >50% drop in metabolic rates and decrease in core body temperature going into winter, which is uncoupled from diet suggesting it may reflect a predictive plastic response (Turbill et al., 2011; Signer 2011). Although there is some evidence of links between IIS/mTOR signalling and hibernation in mammals (Schmidt & Kelley, 2001; Wu & Storey, 2016), we hypothesise that further work is likely to uncover an important role for the pathway.

As well as playing a pivotal role in signalling the onset of diapause, we anticipate that IIS/mTOR and associated pathways are also involved in bringing the organism out of diapause or triggering the onset of physiological remodelling in preparation for growth/reproduction under favourable conditions (Flatt et al., 2013; Hut et al., 2014). On both sides of this response, timing the physiological switch to accurately coincide with either the onset of challenging environmental conditions (e.g. winter or dry season) or of favourable conditions for reproduction (e.g. spring or wet season) is likely to have major impacts on fitness and be under strong selection (e.g. Salis, 2018).

Importantly, this broad perspective does not restrict the adaptive significance of predictive plasticity produced by the IIS pathway to deep physiological switches associated with seasonal or annual changes in the environment. It is well established in the laboratory that repeatedly switching the dietary treatment of flies causes very rapid, reversible changes in their mortality rates, consistent with acute and readily reversible responses of the underlying pathways to changes in dietary cues (Catterson et al., 2018; Mair, Goymer, Pletcher, & Partridge, 2003). To us, this suggests that this response and the pathways involved have evolved not just to indicate broad seasonal or annual shifts in the environment, but also much more immediate, fine-scale variation in conditions. We expect natural selection to favour genotypes capable of matching growth and reproductive investment to prevailing local conditions, so plasticity in the anabolic/catabolic axis could be adaptive even over very fine spatial and temporal scales. Here, Adler & Bonduriansky's (2014) idea that a DR-like response could maintain reproductive function in the face of sub-optimal conditions seems relevant. Imagine a temperate herbivore population in early spring which experiences considerable spatial variation in habitat quality and food availability. Here, the ability to fine-tune the degree to which physiology switched towards anabolic processes in spring to match local conditions might be crucial in allowing individuals to reproduce with limited resources. If poor conditions are predictive of increased mortality risk, the fitness pay-off of managing to reproduce under duress at potential cost to future survival will be even greater.

This example is simply an attempt to illustrate how the IIS pathway could be selected to both promote survival at a cost to reproduction (RRH), or current reproduction at the expense of subsequent survival and reproduction (Adler & Bonduriansky, 2014), depending on the precise environmental cues and the relative fitness costs and benefits of reproducing now versus reproducing later in a given environment. The point is

653 that, under our much broader conceptualisation of the cues and selective pressures shaping IIS as a pathway
654 underpinning adaptive predictive plasticity, apparently competing explanations for the evolution of the
655 pathway become complementary. A major question, if our hypothesis is correct, is how the physiological
656 response induced by the IIS pathway varies depending on the strength and nature of the multivariate
657 environmental cue. We would predict that sustained, multiple cues (including photoperiod cues) would be
658 required to trigger deeper physiological changes such as development/reproductive diapause and
659 hibernation, whilst acute cues (including singular cues like just diet) could trigger much more subtle
660 responses which might act to preserve reproductive function or optimise timing of the onset of reproduction
661 and growth.

662 So how does all this explain or relate to the observation that feeding lab organisms reduced calories (or
663 protein specifically) extends lifespan? The *ad libitum* or high protein diets of 'control' animals in DR
664 experiments are highly artificial and may poorly reflect the diets these animals have evolved to consume
665 under natural conditions. The handful of available studies comparing effects of DR and IIS/mTOR on lifespan
666 under standard versus more naturalistic laboratory conditions suggest results do not necessarily generalise
667 (Briga & Verhulst 2015). As has been widely discussed, DR conditions may be much closer to a state that is
668 actually experienced by wild animals, although we expect most wild animals to live under highly variable
669 environments and experience conditions ranging from sufficient or excess nutrient availability through to
670 starvation conditions. We argue that what we observe in laboratory models in DR experiments is a response
671 of these pathways to a single, weak environmental cue which is not accompanied by the wider environmental
672 pressures it might be predictive of under natural conditions. Under entirely benign conditions in the lab, the
673 switch towards anabolism, autophagy and cellular recycling under DR is unsurprisingly associated with
674 increased lifespan and a reduction in forms of accumulated damage involved in ageing. Ad lib fed animals in
675 the lab will show greater cell growth and proliferation rates, accumulate more damage as a result, but may
676 also experience various forms of pathology associated with unnaturally high nutrient/protein intake which
677 may also reduce lifespan. In the wild, responses to diet in these pathways occur ahead of or alongside a suite
678 of environmental pressures. We hypothesise that the IIS/mTOR pathways have evolved and been conserved
679 because they provide an adaptive mechanism to deal with those pressures. Lifespan extension in the lab

under DR does nothing to address this hypothesis, because the pathways are triggered without the accompanying environmental challenges they have evolved to predict. This highlights our limited understanding of the real evolutionary function of IIS/mTOR pathways under natural conditions, and the need for evolutionary ecologists to consider how predictive plasticity, life history, and ageing coevolve under variable environments.

6. Testing the Hypothesis

We have proposed that the IIS/mTOR pathways have evolved to integrate multiple, important environmental cues and trigger changes in physiology that promote organismal fitness in complex, variable natural environments. In this section, we consider ways in which the perspective and ideas presented above could be taken forwards. First, we consider their implications for studies of DR and IIS/mTOR effects under laboratory conditions and how current experimental paradigms might be adapted to address whether and how diet related cues interact with other kinds of environmental cues to impact fitness in the laboratory. Next, we consider the need for more theory to help us understand how natural selection might shape the co-evolution of plasticity, life history and ageing under variable environments. The nature of the costs of plasticity are central to any such theoretical treatment and we consider evidence that there might be costs to DR response and activation of the IIS/mTOR pathway. Finally, we consider the prospects of studying and testing these ideas in wild animal populations, which will ultimately be crucial to establish the real fitness costs and benefits of variation in IIS/TOR pathway expression and plasticity.

6.1. An evolutionary ecology approach to DR and IIS/mTOR in the lab: One valuable change of approach that could be taken in biogerontology studies is a reconsideration of the way we frame questions relating to DR, to better understand the role for IIS/mTOR in the responses to a variety of environmental challenges, and how this informs evolutionary theories about plasticity. Table 2, below, outlines the general testable hypotheses emerging from our framing of the IIS/mTOR pathways as a general form of predictive plasticity, alongside testable predictions emerging from these hypotheses. Below we discuss work already conducted

705 which sheds light on these predictions, although we note that studies directly testing these predictions are
706 very rare in the literature.

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716 Table 2. Hypotheses and predictions emerging from our synthesis of DR and IIS/mTOR pathways as a general
717 form of predictive plasticity that could be tested in the laboratory.

Hypothesis	Prediction
IIS/mTOR respond to and integrate multiple environmental cues.	Combinations of environmental cues (e.g. photoperiod as well as diet) should have different or additive effects on IIS/mTOR signalling and organismal life history.
IIS/mTOR signalling underpins predictive plastic responses.	Disabling the pathways will reduce the ability to respond to the environment and individuals will become less fit under variable environmental conditions.
Plasticity conferred by IIS/mTOR signalling is adaptive.	If we provide environmental insults/stressors without preceding predictive environmental cues (e.g. cold stress with or without prior entrainment to shortened

	photoperiod), signalling will be reduced and the insult will have a greater negative impact on fitness.
Plasticity conferred by IIS/mTOR signalling is costly.	Repeatedly triggering IIS/mTOR pathways (e.g. diet switching, or photoperiod manipulation) without the accompanying environmental pressures these anticipate will result in reduced fitness relative to individuals that have not had pathways triggered.

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725 *Drosophila* would be well-suited to this type of experimental approach, given its well-defined adult
726 reproductive dormancy phenotype, short lifespan, and amenability to genetic manipulation. Cues that can
727 be readily manipulated in the lab include photoperiod, temperature, and diet. Along similar lines,
728 environmental pressures that can be modelled in the lab include severe cold stress, starvation, and infection.
729 One prediction is that IIS mutants should be better able to resist environmental challenges as, in general, IIS
730 signalling is lowered in these contexts. This is indeed the case for in dILP-compromised (MNS cell ablated or
731 *dilp* mutant) flies that demonstrate enhanced starvation resistance (Broughton et al., 2005; Gronke et al.,
732 2010) and for flies where artificial inactivation of insulin producing cells (IPCs) promotes entry to reproductive
733 diapause upon cold stress (Ojima et al., 2018). It is important to note this is not true for resistance to all
734 environmental insults (e.g. heat stress, Broughton et al., 2005) which may be dependent on intact IIS
735 signalling. Importantly, we predict that individuals with attenuated IIS/mTOR would be less able to respond
736 to withdrawal of stress by resuming reproduction. Whether the ability to plastically switch in and out of

reproductive diapause through IIS/mTOR signalling when subjected to environmental insults, ultimately increases reproductive fitness, remains to be tested. These types of studies, in combination with those that manipulate combined cues with or without accompanying stresses, are needed to address whether IIS/mTOR signalling is a form of predictive plasticity responding to multiple cues.

6.2. Co-evolution of plasticity, life history and ageing: The fact that DR and IIS/mTOR network suppression increases lifespan across a range of distantly related laboratory model systems (yeast, nematodes, fruit flies, mice) suggests that these pathways' functions are strongly evolutionarily conserved (Fontana & Partridge, 2015). However, recent studies have also found functional divergence among species and populations in IIS/mTOR genes and signatures of directional selection shaping this divergence. For instance, McGaugh et al. (2015) compared genes and protein structure from the IIS/mTOR network and showed that hormones and receptors in the network were likely targets of clade-specific selection between reptiles and mammals with a potentially important role in the distinct adaptations of physiological and life history among those vertebrate groups. Studies comparing genetic diversity among human populations also suggest the IIS/mTOR network has been under strong directional selection (Luisi et al., 2012), whilst a study of wild-derived nematodes found a signature of a recent selective sweep at the *age-1* gene (Jovelin, Comstock, Cutter & Phillips, 2014). Studies examining allelic variation in the *InR* gene in *Drosophila melanogaster* have similarly identified strong signals of selection, and have identified specific alleles which are more prevalent at high latitudes and during winter which are associated with reduced IIS signalling and greater cold and starvation resistance in the laboratory (Paaby, Blacket, Hoffmann & Schmidt, 2010; Paaby, Berglund, Behrman & Schmidt, 2014). The mounting evidence from among-species and -population variation in genes in the IIS/mTOR pathways is mirrored by evidence that the DR response varies among genotypes in laboratory model organisms (Dick et al., 2011; Liao, Rikke, Johnson, Diaz, & Nelson, 2010; Schleit et al., 2013; Stastna, Snoek, Kammenga, & Harvey, 2015), and that the effect of DR on lifespan and reproduction varies among species (Moatt, Nakagawa, Lagisz, & Walling, 2016; Nakagawa, Lagisz, Hector, & Spencer, 2012). Generally, this highlights the importance moving beyond questions relating to the conserved functions of the IIS/mTOR pathway and towards a broader understanding how and why natural selection has and continues to act to shape variation in this network of genes and in the response to DR. Furthermore, we need to more carefully

764 consider how genetic variation in the IIS/mTOR pathways influence phenotypic plasticity, rather than solely
765 local adaptation. The key to this lies in developing a coherent theoretical framework for how adaptive,
766 reversible forms of plasticity – which we argue here is what DR and IIS/mTOR pathways effects on lifespan in
767 the laboratory reflect – coevolve with variation in life history and ageing rates.

768 Evolutionary theory has tended to consider adaptive plasticity as evolving against a backdrop of a particular
769 kind of life history, rather than examining how plasticity and life history might co-evolve (Ratikainen & Kokko,
770 2019). As discussed above, evolutionary explanations for the DR response have tended to focus on life history
771 trade-offs, ignoring the evolutionary factors known to shape plasticity. That said, several interesting recent
772 theoretical studies have started to explore the interface between plasticity, life history and ageing (Fischer
773 et al., 2014; Ratikainen & Kokko, 2019). Ratikainen & Kokko (2019) show that in relatively predictable
774 environments, with large environmental fluctuations, in which costs of phenotype-environment mismatch
775 are high, highly reversibly plastic phenotypes are expected to coevolve with longer lifespans, whilst shorter
776 lived and less plastic life histories evolve under more unpredictable conditions. Importantly, the expression
777 of plasticity can be age-dependent and plasticity itself may play an important role in ageing. Fischer et al.
778 (2014) showed that age-dependent plasticity can evolve as an adaptation to the acquisition of more reliable
779 environmental information over time and age-dependent changes in the fitness pay-offs of switching
780 phenotypes to match environmental conditions. Their models predict a decline in plasticity with age, which
781 a recent laboratory study of fish found support for (Meuthen, Baldauf, Bakker, & Thunken, 2018). Cotto &
782 Ronce (2014) showed that the weakening of selection with age can lead to a maladaptation to local
783 environment in older individuals (Cotto & Ronce, 2014). Although framed in the context of local adaptation
784 and not plasticity, their models imply that a breakdown in adaptive plasticity in later life could play a role in
785 senescence in natural populations. We are still a long way from a complete or coherent theoretical
786 framework for understanding how plasticity, life history and ageing interact, but these emerging studies
787 highlight key, neglected evolutionary variables which we must consider and quantify when thinking about
788 IIS/mTOR pathways regulate reversible adaptive plastic responses. Critically, these include the predictability
789 of the environment, the reliability of information organisms can gather about the environment, the age-
790 dependent fitness pay-offs associated with a plastic response, and the fitness costs of plasticity itself.

6.3. Costs of plasticity: As mentioned above, evolutionary theory usually assumes that predictive plastic responses have fitness costs, but these potential costs have rarely been considered in the context of the plasticity conferred by the IIS/mTOR network. While it has been demonstrated that inhibition of the network will have costs in terms of reduced reproduction and growth (e.g. Clancy et al., 2001; Tatar et al., 2001) and reduced immune responses such as wound repair (Dirks & Leeuwenburgh, 2006; Hunt et al., 2012), the question of whether the reversible activation of the signalling pathways and the plasticity they induce could themselves have fitness costs has not been directly considered. Interestingly, a recent paper proposed that repetitive seasonal physiological remodelling in long-lived organisms – akin to reproductive diapause, torpor and winter hypometabolism discussed above – could be physiologically costly and a far more important driver and predictor of biological ageing than chronological age (Landes et al., 2017). They empirically supported this hypothesis with an elegant experiment on mouse lemurs, in which physiological responses to seasonal change were induced a variable number of times in the lab using photoperiodic cues. Lemurs which experienced more seasonal changes over the same temporal period had increased age-related mortality risk (Landes et al., 2017). This suggests that the kind of physiological response we are proposing is triggered by IIS/mTOR pathways could have a profound physiological cost and impact fitness and ageing. The idea that the physiological costs of this kind of deep remodelling could actually drive senescence is intriguing, and offers yet another potentially important type of link between plasticity, life history and ageing. Interestingly, work investigating developmental and reproductive diapause in worms and flies suggests these responses do not come at a cost to subsequent lifespan and ageing in the laboratory (Tatar & Yin, 2001), whilst comparative studies suggest hibernating mammals have higher survival and slower life histories than similar sized non-hibernating species (Turbill, Bieber, & Ruf, 2011). While challenging to undertake, further work to understand the fitness costs of seasonal remodelling, hibernation and diapause is important to understand the evolutionary forces shaping this widespread form of plasticity.

Several studies in fruit flies provide some evidence for costs of diet or diapause-related plasticity. Experimental evolution studies of fruit fly populations which vary in the propensity to undergo reproductive dormancy in response to photoperiod and temperature cues do reveal a cost (Schmidt & Conde, 2006). Here, the propensity to show a dormancy response increased across generations under stressful conditions, but

declined under control conditions. The evolutionary loss of diapause under constant, benign conditions strongly implies a fitness cost of this response, which presumably was outweighed by its fitness benefits under challenging conditions (Schmidt & Conde, 2006). Studies of wild flies in North America and Australia have identified alleles of the *InR* gene which vary with latitude and season (Paaby et al, 2010; 2014). Flies with alleles more commonly found at high latitudes and in winter show increased cold/starvation resistance but reduced fecundity and delayed development time compared to lower latitude alleles, suggesting potential fitness costs of reduced IIS signalling (Paaby et al, 2014). Some diet switching studies in fruit flies also provide evidence consistent with a cost of plasticity: groups that experienced repeated switching from high food to DR or vice-versa every 4 days were shorter lived than groups maintained on one treatment or the other (McCracken, Adams, Hartshorne & Simons, 2019). Interestingly, the same study found no effect on lifespan if the switch was performed every 2 days (McCracken et al, 2019) and it has previously been shown that 3 days are required for changes in diet to be reflected in *Drosophila* egg production (Mirth & Piper, 2017). Another fly study found that intermittent fasting (on a 2 days *ad libitum* / 5 days fasting regime) during adulthood increased mortality risk, although a shorter period of fasting in early adulthood followed by ad libitum feeding actually increased lifespan (Catterson et al., 2018). This suggests some sort of time threshold between the onset of environmental change and physiological remodelling, which has also been proposed in other plastic responses to environmental change (e.g. Fricke, Bretman, & Chapman, 2010). Overall, the literature does provide some indication for costs of plastic responses to diet change, season remodelling and diapause but much more research needs to be conducted across species and environments to better understand this crucial factor in the evolution of predictive plasticity.

6.4. Studying in the wild: Ultimately, studies in the wild are the only way to assess the true fitness costs and benefits associated with variation in responses to food availability and expression of IIS/mTOR pathways. Laboratory studies can provide important support for key predictions from evolutionary theory, but are unlikely to realistically capture the way natural selection really operates in complex, variable environments. However, studying diet choice in the wild is a major challenge. Resource abundance and diet have been successfully linked to fitness and behavioural traits in the wild previously. However, these often involve proxy

845 measures (e.g Regan, Pilkington, Pemberton, & Crawley, 2016;Regan et al., 2017) or large scale monitoring
846 of individual feeding (e.g. Felton et al., 2009; Irwin, Raharison, Raubenheimer, Chapman, & Rothman, 2015).
847 Proxy measures, such as abundance of a key resource, do not give any information on actual choice or
848 composition of individual diets. Although monitoring individual intake overcomes this, it is far from simple.
849 There is a high degree of variation between individuals in the wild, with body size, sex and age difference all
850 influencing intake rate. Consequently, any study of intake requires a large number of focal individuals.
851 Furthermore, this monitoring must be done for extended periods of time with estimates for quantity and
852 quality of food ingested (e.g. Irwin et al., 2015; Guo et al., 2018), which can never be as precise as lab studies.
853 Perhaps the biggest challenge of individual monitoring is the difficulty in distinguishing between diet choice
854 and diet constraint – i.e. what an animal would choose to eat and what it can eat. That said, a recent study
855 successfully released diet constraint through supplementary feeding in a wild primate, and showed that diet
856 choice changed in response to seasonal demands on thermoregulation (Guo et al., 2018). In field settings, a
857 further challenge is that any measurement of diet choice will only be representative for the specific
858 environmental conditions at that time and monitoring of diet choice would therefore need to be done across
859 a large number of individuals at multiple time points and seasons. Despite these challenges, a number of
860 studies have successfully applied nutritional geometry in the wild and across different environmental
861 conditions (e.g. Irwin et al., 2015; Guo et al., 2018). We also envisage potential for the application of cutting-
862 edge telemetry to closely monitor space use, behaviour and metabolism (Signer et al., 2011; Fischer et al.,
863 2018) and the application of meta-barcoding of faecal samples to monitor diet choice (Pompanon et al., 2012)
864 to greatly enhance our ability to understand diet choice in wild animals in coming years.

865 A central tenet of the hypothesis proposed here is that conserved endocrine pathways, specifically those
866 associated with IIS/mTOR, are critical to the response of wild animals to variation in their environment. This
867 opens the possibility of directly assess variation in key hormones (e.g. IGF-1) or IIS-associated gene expression
868 patterns in wild animals and relating this to environmental conditions and fitness. Both can be measured
869 through non-lethal blood sampling, and a growing number of recent studies demonstrate the potential for
870 studying selection on hormone variation, including IGF-1, in wild animals using such an approach.
871 Comparative studies have documented interesting relationships between circulating IGF-1 levels and life

history variation across species of birds and mammals (Swanson & Dantzer, 2013; Lodjak, Mand & Magi, 2018). Measurement of IGF-1 in samples collected as part of individual-based studies of wild vertebrates further document associations between the hormone and body mass, growth rates, reproduction and survival (Addis, Gangloff, Palacios, Carr & Bronikowski, 2017; Sparkman, Byars, Ford & Bronikowski, 2010; Lewin, Swanson, Williams & Holekamp, 2017; Lodjak, Tilgar & Magi, 2016; Lodjak, Magi, Sild & Mand, 2017). Intriguingly, a recent correlational study of spotted hyenas found that high levels of IGF-1 as a juvenile predicted higher juvenile body mass and, indirectly via body, increased survival to maturity but also reduced adult longevity (Lewin et al., 2017). However, most studies to date in wild systems have focussed on the relationships between IGF-1 levels and life history traits with far less attention paid to the response of IGF-1 and associated components of the IIS/mTOR pathway to environmental variation.

Under the hypothesis laid out above, changes in the environmental cues should be reflected in the activity of the pathways themselves. Furthermore, repeated measures could be taken across ecologically relevant timescales, to assess the plasticity of responses and how organisms are remodelling in response to environmental cues. These could also be done across a wide range of individuals of different ages and in both sexes, as well as tracking the same individual for the entirety of their lifespan, potentially shedding light on how these processes change with age in a natural setting. Long-term individual-based studies in the wild linking IGF-1, environment, age and fitness could allow us to address how these pathways vary with environment and host genotype under natural conditions, as well as how natural selection actually shapes variation in plasticity associated with the IIS/mTOR pathway.

7. Conclusions

We have proposed that the IIS/mTOR pathways respond to a variety of cues indicative of environmental quality, which result in physiological changes to promote fitness in variable environments. Whilst many previous studies have hypothesised that IIS/mTOR underpin an important form of adaptive plasticity, we have sought to synthesise and generalise this idea based on current empirical data and develop a framework for testing the pathways' evolutionary origin and function from the perspective of predictive plasticity. We

would emphasise the importance of multi-disciplinary perspectives on DR and IIS/mTOR pathway effects on health, fitness and ageing going forward. Mechanistic insights from fields like biogerontology can help ecologists and evolutionary biologists identify and understand important physiological pathways underpinning life history and fitness variation in the wild. Equally, biogerontologists can benefit from taking an evolutionary perspective and considering how and why the IIS/mTOR pathways and DR response evolved. An evolutionary and ecological perspective can crucially shed light on the significant within and among species variation in both the DR response and IIS/mTOR pathways, which is often overlooked by biogerontologists and may have important implications for how intervention may influence health and lifespan outside of the laboratory.

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Figures legends

Figure 1. Conserved signalling through IIS/mTOR regulates anabolic and catabolic processes. Akt (or protein kinase B): a serine/threonine-specific protein kinase; FOXO (Forkhead box O): transcription factor; IGF/R: insulin-like growth factor / receptor; ILP: insulin-like peptide; PI3K: Phosphoinositide 3-kinase; Rheb: a Ras-family GTP-binding protein; TSC1/2: Tuberous sclerosis proteins 1 and 2; TORC1: target of rapamycin complex 1. Yellow text: *C.elegans* protein homolog; green text: *D.melanogaster* protein homolog; blue text: *M.musculus* protein homolog.

Figure 2. Multiple environmental inputs signal through IIS/mTOR to regulate multiple physiological processes.